UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/978,333	10/15/2001	Peter M. Glazer	YU 132 (OCR 653)	4662

23579 7590 05/10/2005

PATREA L. PABST
PABST PATENT GROUP LLP
400 COLONY SQUARE
SUITE 1200
ATLANTA, GA 30361

EXAMINER	
MYERS, CARLA J	
ART UNIT	**PAPER NUMBER**
1634	

DATE MAILED: 05/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/978,333	GLAZER, PETER M.	
	Examiner	Art Unit	
	Carla Myers	1634	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *7-12 and 15-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *7-12 and 15-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

HC

DETAILED ACTION

1. This action is in response to the amendment filed March 1, 2005. Applicant's arguments have been fully considered but are not persuasive to overcome all grounds of rejection. All rejections not reiterated herein are hereby withdrawn. This action is made final.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 7-12 and 15-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for targeted recombination of a target nucleic acid molecule in vitro or ex vivo wherein the methods comprise contacting a target nucleic acid molecule or an isolated cell with a triple helix forming oligonucleotide (TFO) and a donor oligonucleotide that is complementary to a target nucleic acid sequence, forming a triple helix by hybridizing the TFO to the target nucleic acid, and recombining the donor oligonucleotide into the target nucleic acid to thereby accomplish targeted recombination of the target nucleic acid, wherein the TFO has a Kd of less than 2×10^{-7}, does not reasonably provide enablement for method of in vivo targeted recombination or methods of targeted recombination in which a TFO is utilized which has a Kd of more than 2×10^{-7}. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors have been considered in formulating this rejection (*In re Wands,* 858F.2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988): the breadth of the claims, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, the amount of direction or guidance presented, the presence or absence of working examples of the invention and the quantity of experimentation necessary.

The claims are drawn to methods of targeted recombination wherein the methods comprise providing a triple-helix forming oligonucleotide (TFO) to a target double-stranded molecule and a donor nucleic acid. The TFO has the property of having a Kd of 2×10^{-7} or less with the target nucleic acid. The donor nucleic acid may be tethered or unlinked to the TFO and recombines into the target nucleic acid sequence. The claims as written are inclusive of methods which are performed in vitro and methods which are performed in vivo (see page 3 of the specification). In particular, claim 10 allows for the use of the targeted recombination to alter the activity of a protein encoded by the target double-stranded nucleic acid. Claims 15-24 are inclusive of methods in which recombination produces a change in the genome of an intact human or animal. While the specification has enabled methods for in vitro and ex vivo targeted recombination using a donor nucleic acid tethered or unlinked to a TFO having a Kd of 2×10^{-7}, the specification has not enabled methods for in vivo targeted mutagenesis.

The specification exemplifies the in vitro treatment of cells and cell extracts with triple-helix forming oligonucleotides and teaches that oligonucleotides having a Kd of 2×10^{-8} or less are capable of inducing mutations in vitro at a rate of 0.2-0.8% (see

Example 1 in the specification). An oligonucleotide having a Kd of 3×10^{-5} (AG10) induced mutations at a frequency of .07 as compared to the frequency of .03 induced by an oligonucleotide that did not show significant binding. The specification also teaches that HeLa cell-free extracts treated with the AG30 TFO tethered to or unlinked to a SupFg1 donor fragment had a recombination frequency of 45×10^{-5} and 40×10^{-5}, respectively.

However, the specification has not enabled methods for targeted recombination in vivo or methods in which targeted recombination produces changes in the genome of an intact animal or human. The specification does not exemplify the in vivo use of TFOs/donor fragments, particularly the in vivo use of these oligonucleotides for the purposes of targeted mutagenesis. The activity of triple-helix forming oligonucleotides in vivo is unpredictable in the absence of in vivo data because the success of the therapy is dependent on adequate concentrations of the oligonucleotide reaching the desired site in vivo, hybridizing the TFO to a specific gene sequence, and recombining the donor fragment into the target gene sequence. Specifically, in vivo oligonucleotide therapies are unpredictable for the following reasons: (I) The triple-helix forming oligonucleotide may be degraded in blood and tissues under physiological conditions and therefore may not reach the target site; (ii) The ability of the oligonucleotide to be taken up by the cell is expected to be different under physiological conditions as versus tissue culture, i.e. the permeability of the cell would be different under physiological conditions and would be expected to vary with cell type; (iii) It is not clear what would be the optimum concentration of the oligonucleotide required for effective treatment, the

mode of administration and the pharmacokinetics of therapy; (4) The ability of the oligonucleotide to form a triple helix under physiological conditions is unpredictable since the formation of the triple-helix varies significantly with oligonucleotide length, and chemical composition and is highly affected by the presence of secondary and tertiary nucleic acid structures; and (5) the ability of the donor oligonucleotide to bind to and recombine with the target nucleic acid varies significantly with the length and chemical composition of the donor oligonucleotide and the recombination process is also affected by secondary and tertiary nucleic acid structures. Therefore, for each therapeutic oligonucleotide, one must develop de novo the appropriate set of parameters for in vivo function. While the specification provides a general discussion regarding the administration of TFOs in combination with donor oligonucleotides, there is insufficient guidance provided in the specification as to how to use any particular oligonucleotides for therapeutic purposes in vivo and therefore one is left to develop de novo the appropriate techniques for selection, delivery and effective use of each therapeutic oligonucleotide. In view of the unpredictability in the art of oligonucleotide therapeutics, the skilled artisan would not accept that results obtained in vitro are reasonably predictive of the results obtained in vivo for because the correlation between in vitro and in vivo results is not a general characteristic that can be applied to each and every pharmaceutical composition and the record has not established a universal correlation between the results obtained in vitro with triple-helix forming oligonucleotides and the results obtained in vivo. Moreover, for triple-helix forming oligonucleotides which induce mutagenesis, the ability to use such oligonucleotides in vivo is further unpredictable

because there is no means to predict a priori where a mutation or what particular mutation will occur.

Further, Wang (page 804; Science. 1996. 271: 802-805; cited in the IDS) teaches that the triple-helix forming oligonucleotides induce a scattered spectrum of mutations, rather than specific mutations. As discussed in the specification, targeted mutagenesis is performed to achieve the result of activating, inactivating or altering the activity and function of a gene. However, the process of targeted mutagenesis with triple-helix forming oligonucleotides does not result in a single, specific mutation. Rather, this process, as exemplified in the specification, results in the formation of an array of point mutations and deletions at or surrounding the region to which the oligonucleotide binds. While the donor oligonucleotide may be used to introduce a specific sequence into the target nucleic acid, the binding of the TFO also introduces an array of nonspecific mutations at the target site or adjacent thereto. For therapeutic purposes, the induction of random mutations would not provide an art recognized acceptable means for the treatment of a disease because there is no predictable means for determining which mutations would have a null effect and which mutations may actually result in the inappropriate stimulation or inhibition of gene expression.

It is also highly unpredictable as to whether the TFO/donor oligonucleotide would be capable of inducing a sufficient amount of recombination and mutations in a sufficient quantity of cells to impart a therapeutic effect in view of the fact that the specification teaches that even in vitro such TFOs tethered to a donor fragment induce recombination at a frequency of 45×10^{-5} and TFOs not linked to the donor fragment

induce recombination at a frequency of 40 x 10^{-5}. Moreover, in view of the cellular mechanisms for repairing mutations, it is highly unpredictable as to whether a sufficient number of cells would maintain the mutation and pass the mutation on to secondary cells in order to allow for an effective therapy. Further, The specification teaches that in mice treated with AG30 (no donor fragment provided), mutagenesis was observed in liver, skin, kidney, colon, small intestine and lung cells at a frequency five fold that of background (see Example 7). However, the specification does not teach the frequency at which recombination is achieved in intact animals or humans.

At the time the invention was made, it was well recognized in the art that significant experimentation would required to practice the in vivo administration of triple helix forming oligonucleotides. For example, Wang (Molecular and Cellular Biology, 1995, p. 1767; cited in the IDS) states that "(c)learly, forming a triple helix in vitro under controlled buffer conditions is an easier task than doing so in vivo with exogenously added oligonucleotides, which must be taken up by the cells, enter the nuclei, and bind to the target site under suboptimal conditions". Wang (p. 1767) goes on to state that "(t)heoretically, targeted mutagenesis and inactivation of selected genes might also eventually have therapeutic applications. However, the general applicability of this approach will depend on the extension of the third-strand binding code and the development of nucleotide analogs so that triple helix formation is not limited to polypurine sequences." Yet, there is no specific guidance provided in the specification as to how to overcome the numerous known and unknown obstacles associated with in vivo targeted recombination and mutagenesis with TFOs and donor oligonucleotides,

and as evidenced by Wang, excessive experimentation would be required to accomplish the successful in vivo application TFO/donor oligonucleotides that are capable of targeting specific sequences in vivo.

The teachings of Chan (Journal of Biological Chemistry. 1999. 274: 11541-11548; cited in the IDS) also emphasize the fact that additional research is required before TFOs tethered to donor oligonucleotides can be used in vivo. In particular, Chan concludes that "The TD-TFO approach as a method for DNA sequence modification has the potential to be useful a research tool and may eventually provide the basis of a gene therapy strategy."

Barre (PNAS (2000) 97:3084-3088; see abstract) emphasizes the requirement for mutagenesis to occur at a sufficient frequency in order for TFOs to be effective in vitro or in vivo. Barre (page 3088) states that "If this value is taken to represent the expected maximal frequency of mutations on an endogenous target, the proportion of targets reached by the TFO thus can be estimated as one in a thousand – a proportion too low to envision any therapeutic applications."

The unpredictability in the art of using TFOs in vivo is further highlighted by Seidman et al (The Journal of Clinical Investigation. August 2003, 112: 487-494). This reference (which is co-authored by the present inventor) teaches that "Biological applications of TFOs are compromised by fundamental considerations, as well as limitations imposed by physiological conditions....triplex formation involves conformational changes on the part of the third strand, and some distortion of the

underlying duplex. Pyrimidine motif triplexes are unstable at physiological pH because of the requirement for cytosine protonation that occurs at relatively acidic pH (pKa = 4.5)...All of these factors impose kinetic barriers on triplex formation and reduce the stability of triplexes once formed" (pages 487-488). With respect to the importance of the stability of binding, Seidman (page 488) teaches "TFOs with equilibrium dissociation constants of approximately 10^{-9} M were active; those with Kd's of 10^{-6} M were not." The reference concludes that "It seems likely that recent advances in oligonucleotide chemistry have considerable potential for the development of TFOs with robust gene targeting activity. This will require coordinated effort between chemists and biologists, but recent data suggests that this effort will be rewarded." Accordingly, the teachings of this reference indicate that even as of 2003, additional research is required before TFO/donor oligonucleotides can be used for in vivo applications.

In summary, there is insufficient guidance provided in the specification as to how to use the claimed TFOs/donor oligonucleotides for in vivo applications. The specification as filed provides only general guidelines for the administration of TFOs and donor oligonucleotides, leaving one to develop de novo the appropriate techniques for in vivo delivery and effective use of the broadly claimed methods. Accordingly, in view of the breadth of the claims, the recognized unpredictability in the art of targeted recombination and mutagenesis and in the art of the in vivo administration of TFO/donor oligonucleotides, and in view of the lack of working examples in the specification, it would require undue experimentation for one of skill in the art to practice the invention as broadly claimed.

RESPONSE TO ARGUMENTS:

In the response, Applicants traverse this rejection by stating that the claims as amended are fully enabled by the specification. It is stated that pages 15-27 of the present specification describes targeted mutagenesis by TFOs in vivo in monkey COS cells, patient derived XPA cells, patient XPV cells and normal human fibroblasts. However, each of the above are examples of in situ / ex vivo targeted mutagenesis and are not examples of in vivo (in an intact animal or human) targeted mutagenesis. For the reasons set forth in the above rejection, the skilled artisan would not accept that results obtained in vitro/ in situ / ex vivo are reasonably predictive of the results that would be obtained in vivo.

Applicants point to Example 7 of the specification as teaching that in mice treated with TFOs, mutagenesis was observed in liver, skin, kidney, colon, small intestine and lung cells at a frequency of 5 fold above background. However, these results were obtained using the AG30 TFO alone (i.e., in the absence of a recombination donor fragment). No results are provided in the specification for the use of a TFO in combination with a donor fragment in an intact human or animal. Further, the results set forth in Example 7 do not specify whether mutagenesis was specific or random. It is unclear and unpredictable as to how the artisan could use a method of randomly mutating the genome of an intact human for practical purposes.

Applicants cite several references as demonstrating that TFOs can produce inheritable changes in intact animals. However, the cited Luo reference teaches the use

of TFOs in isolated mouse cells. Faruqi teaches the use of TFOs in isolated monkey COS-7 cells. Seidman provides a review of papers teaching triplex-induced recombination and discusses the use of TFOs to induce recombination in isolated COS cells and human cell free extracts. None of the cited references teaches the use of TFOs in combination with donor fragments to induce triple helix formation and recombination in intact animals or humans.

Applicants state that in contrast to the examiner's statements, the key finding of Wang is that binding of TFOs in vitro is correlated with intracellular activity. However, the claimed methods are not limited to ones which are performed in situ or ex vivo. Rather, the claims encompass methods that are performed in vivo. The teaching that a TFO binds to a target site intracellularly does not lead to the conclusion that such a TFO, when administered in vivo, will thereby reach the specific target cell, bind to the DNA within the cell with the required specificity, induce recombination to an acceptable level and generate a specific recombination event within the targeted cells.

Applicants point to Chan as teach an "in vivo protocol." However, Chan does not teach the in vivo use of TFOs. Chan teaches only the use of TFOs in isolated COS-7 cells. Again, it is noted that Chan emphasizes that the TFO technology currently has use only as a research tool, although it may eventually provide the basis of a gene therapy strategy.

Applicants state that Barre teaches that TFOs can be used to modify an endogenous target. However, the teachings of Barre are also directed to only the in vitro

use of TFOs. Further, Barre emphasizes that the efficiency of mutagenesis was too low for therapeutic purposes in an in vitro settings, let alone in in vivo settings.

Applicants further assert that Seidman describes several in vivo studies demonstrating the ability of TFOs to induce targeted recombination. However, Seidman does not in fact provide any examples or data of the in vivo use of TFOs/donor nucleic acids in intact animals or humans.

Applicants assert that the cited papers and the teachings in the specification show that low frequency recombination is sufficient for efficacy. However, the specification and the cited references do not demonstrate the in vivo use of TFOs for the purposes of inducing recombination at an acceptable level in an intact human or animal. Further, there is nothing in these teachings which would lead one to conclude that the results obtained in vitro can be extrapolated to in vivo. A showing that a TFO induces recombination in vitro is not equivalent to demonstrating or establishing the ability to use a TFO/donor nucleic acid in vivo for the purposes of creating a mutation or correcting a specific mutation. Simply inducing recombination in a cell is not enough. The recombination event must be specific and must occur at a sufficient level to yield some benefit. Otherwise, there is no patentable use for the method of in vivo targeted recombination.

3. Claims 15-24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. Claims 15-24 are indefinite because it is unclear as to what is intended to be the relationship between the single-stranded oligonucleotide and the donor nucleic acid recited in claims 15-24, and the single-stranded oligonucleotide and donor nucleic acid recited in claim 7, from which claims 15-24 depend. It is unclear as to whether the oliogonucleotide and donor nucleic acid recited in claims 15-24 is the same as or different from the single stranded oligonucleotide and donor nucleic acid recited in claim 7. While the claims have been amended to recite providing the single-stranded oligonucleotide, providing a donor oligonucleotide and administering the single-stranded oligonucleotide to an intact animal, it is unclear as to whether the providing steps are performed in addition to the administering step or if the administering step further defines the providing step. Since the providing step is said to result in recombination of the donor nucleic acid as a consequence of triple helix formation, it is unclear as to how the providing step is considered to be performed in addition to the administering step. Further, the claims do not recite that the donor nucleic acid is administered into the intact human or animal. Thereby it is unclear as to how recombination of the donor nucleic acid with the target nucleic acid is induced unless the donor is also administered to the intact human or animal or unless the providing step allows for both providing the oligonucleotide and donor and separately administering both an oligonucleotide and donor to an intact animal and human. Accordingly, the claims should be amended to recite, for example, that the providing step comprises administering the single stranded oligonucleotide and donor to the intact human or animal.

B. Claim 19 is indefinite. The claim recites the use of an exogenously supplied DNA fragment. However, it is unclear as to whether the exogenously supplied DNA fragment is the same as or different from the donor nucleic acid. In the later case, it is unclear as to how both the exogenously supplied DNA fragment and the donor nucleic acid are utilized in the method of targeted recombination. Similarly, claim 20 is indefinite over the recitation of "a tethered DNA fragment" because it is unclear as to what is intended to be the relationship between the tethered DNA fragment, the exogenously supplied DNA fragment and the donor nucleic acid and it is unclear as to how this claim is intended to further limit the claimed method.

RESPONSE TO ARGUMENTS:

In the response Applicants state that the rejections have been overcome by the amendment to the claims. In particular, it is stated that the rejection over claims 15-24 has been overcome by the amendment to recite that the oligonucleotide is administered to the intact human or animal. However, the claims remain indefinite because it is unclear as to what is intended to be the relationship between the providing and administering steps, particular in view of the fact that the claims recite both providing and administering the single-stranded oligonucleotide, but recite only a step of providing the donor nucleic acid. With respect to claims 19-20, Applicants state that the rejection has been overcome by the amendment to recite "donor nucleic acid." However, as amended it is unclear as to whether the donor nucleic acid previously recited in the claims is the same as the exogenously supplied donor nucleic acid of claim 19 or the tethered donor nucleic acid of claim 20.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 7-12, 15-21, 23-25 are rejected under 35 U.S.C. 102(b) as being anticipated by Chan et al (Journal of Biological Chemistry. 1999. 274: 11541-11548; cited in the IDS).

Chan et al (see, for example, page 11542) teach a method of targeted recombination wherein the methods comprise contacting a cell with a single stranded TFO tethered or unlinked to a donor oligonucleotide under conditions in which the TFO forms a triple helix with a target nucleic acid and the donor oligonucleotide recombines into the target nucleic acid. In particular, Chan teaches that the combination of TFOs and donor oligonucleotides were able to mediate gene conversion or correction in the supF reporter gene (see page 11545). In particular, Chan teaches that the TFO (AG30) is single stranded, 30 nucleotides in length and comprises polypurine and polypyrimidine nucleotides (see page 11543 and Figure 2). AG30 has a Kd of 3×10^{-8} and the TFO tethered to the donor nucleic acid (A-AG30) has a Kd of 5×10^{-8} (see page 11543). With respect to claims 12 and 25, Chan teaches that the donor nucleic acid is 40 or 44 nucleotides in length (see page 11543). With respect to claims 15-21 and 23-24, the method of Chan is one in which the introduced genomic change could be used

to pass the genomic change onto daughter cells in an animal. With respect to claim 17, Chan teaches transfection of oligonucleotides into cells using LipofectAmine and teaches in vitro triplex formation in a binding buffer, and thereby is considered to teach providing the TFO in a physiologically acceptable carrier. Accordingly, the method of Chan is considered to anticipate the claimed method of targeted recombination.

RESPONSE TO ARGUMENTS:

In the response of March 1, 2005, Applicants state that the present invention is entitled to a priority of 1995 and therefore Chan is not available as prior art. It is stated that support for the present invention may be found in patent '376 and '426. In particular, Applicants point to the '376 patent at column 6 as teaching that a TFO may be administered in combination with a DNA fragment. It is also stated that columns 6 of the '376 patent provides support for the concept of psoralen-linked oligonucleotides and thereby provides basis for the concept of linking a reactive moiety to the TFO.

Applicants arguments have been fully considered but are not persuasive to overcome the present grounds of rejection. It is maintained that the present invention as it is broadly directed to a method for administering both a TFO and a donor nucleic acid does not have basis to the '376 or '426 patents. A claim as a whole is assigned an effective filing date, rather than the subject matter within a claim being assigned individual effective filing dates. In the present situation, the '376 and '426 patents provide basis only for the specific concept of separately providing the TFO and donor nucleic acid. The patents do not provide basis for the concept of a donor nucleic acid

tethered or linked to the TFO. The teachings in '376 regarding linkage of psoralen to the TFO are distinct from a teaching of linking the donor nucleic acid to the TFO. Psoralen is chemical compound which intercalates between DNA and when linked to the TFO acts as a mutagen. The '376 patent does not provide basis for the more general concept of linking any mutagenic compound to the TFO and particularly does not provide basis for the concept of linking a donor recombinant nucleic acid fragment to the TFO. Further, the '426 patent does not provide basis for the recitation in the amended claims of a Kd of less than or equal to 2×10^{-7}. The response points to column 5 and 9 of '426 as providing support for this concept. However, column 5, lines 1-3 of the '426 patent teaches that the Kd is less than or equal to approximately 10^{-7} and preferably the Kd is less than or equal to $2x10^{-8}$. Column 9 of the '426 patent teaches TFOs having a Kd of 3×10^{-5}, 3×10^{-7}, or $2. \times 10^{-8}$. While the specification provides support for TFOs having these individual Kds (i.e, a Kd of less than or equal to 10^{-7} or $2x10^{-8}$ and TFOs having a Kd of 3×10^{-5}, 3×10^{-7}, or 2×10^{-8}), the specification does not provide support for the specific concept of TFOs having a Kd of less than or equal to 2×10^{-7}. Additionally, with respect to the dependent claims, the '426 patent does not provide basis for the concept of TFOs having a length that is between 10 and 60 nucleotides. The '426 patent provides support only for TFOs of 7 to 40 nucleotides, 10-20 nucleotides, 20-30 nucleotides or of 10, 20, 30 or 57 nucleotides (see column 3, lines 66-67 and column 4, lines 1-3, and columns 7-8). There is also no basis for the donor nucleic acid having a length of at least 30 nucleotides or a length of 10 to 40 nucleotides (see present claims 12 and 25). Additionally, while the '426 patent provides support for

TFOs that target the xeroderma pigmentosum gene, the '426 patent does not provide support for TFOs that target the hemoglobin, cystic fibrosis, hemophilia or excision repair pathway genes (see present claim 22). Accordingly, it is maintained that the present invention is entitled to the filing date of October 15, 2001 and thereby Chan is in fact prior art to the claimed invention.

Claim Rejections - 35 USC § 103

6 . The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claim 22 is rejected under 35 U.S.C. 103(a) as being unpatentable over Chan et al (Journal of Biological Chemistry. 1999. 274: 11541-11548).

The teachings of Chan are presented above. Chan does not specifically exemplify methods in which targeted recombination is performed using a xeroderma pigmentosum gene. However, Chan teaches that in combination donors and TFOs can

be used to introduce or correct a mutation in a targeted nucleic acid (see, for example, page 11542). Chan (page 11546) also teaches that patients with Xeroderma pigmentosum are deficient in the nucleotide excision recognition factor XPA due to mutations in XPA and that TFO stimulated recombination depends on XPA activity.

In view of the teachings of Chan, it would have been obvious to one of ordinary skill in the art at the time the invention was made to have applied the TFO/donor recombination method to the XPA gene in order to generate mutations in this gene which would allow researchers to study how mutations in XPA effect nucleotide excision repair and TFO-stimulated recombination/repair processes.

RESPONSE TO ARGUMENTS:

In the response of March 1, 2005, Applicants traverse this rejection for the same reasons stated in paragraph 5 above. Accordingly, the response to those arguments applies equally to the present grounds of rejection.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carla Myers whose telephone number is (571) 272-0747. The examiner can normally be reached on Monday-Thursday from 6:30 AM-5:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (571)-272-0745.

The fax phone number for the organization where this application or proceeding is assigned is (571)-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866)-217-9197 (toll-free).

Carla Myers
May 3, 2005

CARLA J. MYERS
PRIMARY EXAMINER